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Malnutrition

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Kwashiorkor and Marasmus:
Old Concepts and New Developments

The distinction between the two extreme forms of protein-energy malnutrition, kwashiorkor and marasmus, has been accepted by clinicians for many years. The syndrome of kwashiorkor came to dominate the interests of tropical nutritionists when it was recognized after the Second World War as a major cause of death in young children. Children aged 1–3 years often presented after weaning with the acute onset of œdema and desquamating, dyspigmented skin. Many had thin, red and friable hair and they were apathetic and anorexic. Some cases, particularly in the West Indies, also had hepatomegaly with occasional jaundice. The children's weight was usually below normal, coexisting respiratory and intestinal infections were frequent and specific vitamin deficiencies, e.g. vitamin A deficiency with xerophthalmia, were also found and seemed to increase the mortality rate even further (Waterlow *et al.* 1960). Dr Cecily Williams (1933), working in the Gold Coast, had shown that the syndrome was cured by feeding the child on breast milk; this and the early demonstration of hypoalbuminæmia was in keeping with the concept of a protein deficiency disease. The prompt rise in serum albumin levels on feeding purified casein or amino acids seemed to confirm the specific nature of the protein deficient state (Brock *et al.* 1955).

Marasmus was at this stage largely ignored. The clinical signs were not so florid as those in kwashiorkor and much of the work on nutrition was conducted in the African and Caribbean colonies where kwashiorkor seemed to be more prevalent. In the last ten years, however, marasmus has emerged as a major problem of increasing severity as societies become more industrialized and populations move from rural areas to large urban slums where traditional infant rearing practices are disrupted. The marasmic child is often younger than a child with kwashior and very small for his age; when compared with a normal child the marasmic infant has a marked deficit in both weight and height. Wasting of adipose tissue and muscle occurs to an extraordinary degree. Yet, despite these severe changes, hepatomegaly and œdema are absent, the skin usually appears normal, there are few hair changes and the child is alert and hungry. Although hypoalbuminæmia occurs in some cases the fall in serum albumin is much less than that seen in kwashiorkor. In view of this clinical picture it seemed not unreasonable, therefore, to think of the marasmic child as simply suffering from starvation. Initial attempts to treat marasmic children with diets rich in protein had been disappointing until feeding studies with a range of energy and protein intakes showed that much higher energy supplies were needed for the rapid recovery (Ashworth *et al.* 1968).

The distinction between the two disorders soon proved to be of limited practical use since many children in South Africa, Asia, Central and South America and the Caribbean were presenting with some features of both kwashiorkor and marasmus. This led to the use of the all-embracing term 'protein-calorie malnutrition' (Jelliffe 1959) to include the whole spectrum of disorders. Cases of the intermediate forms of malnutrition, characterized by both œdema and wasting, were classified as 'marasmus-kwashiorkor'. The concept of kwashiorkor as a simple protein deficiency state arising from the plentiful consumption of a carbohydrate-rich, low protein diet also seemed too simple since in some countries, such as India, children developed either kwashiorkor or marasmus on a cereal-based diet, which was qualitatively no different from that of other children in the community (Gopalan 1968). Autret & Béhar

(1954) had also shown that children with kwashiorkor were often consuming a diet poor in energy as well as in protein, and this was later to be confirmed by Rutishauser & Whitehead (1972) in their Ugandan studies on children from a community with a high incidence of kwashiorkor.

Individual Variability in Adaptation to Deficient Diets

These findings led to the suggestion that kwashiorkor was in some way the result of a breakdown in the adaptive process to a shortage of both protein and energy. The marasmic child was thought to respond appropriately by slowly reducing his body reserves of both fat and protein, thereby maintaining for as long as possible the integrity of the visceral tissues and the production of liver proteins, particularly albumin (Gopalan 1968, Waterlow 1968). A diminished response to stress in kwashiorkor was emphasized by the Indian workers who found lower cortisol levels in kwashiorkor than in marasmus; there was also a reduced cortisol response to β-corticotrophin in kwashiorkor. Many studies on animals fed low protein diets had shown that peripheral tissues, such as muscle and skin, were preferentially depleted of protein, with the amino acids from these tissues being redistributed and thereby contributing both to the mass of liver protein and to the production of serum albumin. Detailed studies of the synthesis rates of albumin in marasmic and recovered children also showed that albumin synthesis fell on feeding a low protein diet, but the fall was buffered in a well-nourished child, presumably because of the plentiful supply of amino acids from muscle (Table 1). Thus, by 1968 the problem in understanding kwashiorkor seemed to be one of finding a cause for the breakdown in the adaptive mechanism and for the poor mobilization of peripheral amino acids needed for hepatic albumin synthesis.

Despite this emphasis on adaptation McCance (1968), on the basis of his animal experiments and further contact with the 'pure' form of kwashiorkor in Uganda, reiterated the concept of kwashiorkor as a disease resulting from the ingestion of a

protein-deficient diet and classified marasmus as a disease of starvation. There was thus a clear need to assess both the nutrient intakes of children prone to the two forms of malnutrition and to assess the individual responsiveness of children to changes in their diet and to other factors in their environment. Only in this way would one be able to distinguish between dietary causes and metabolic differences between individuals as the key factors determining the progression of malnutrition to a state of either kwashiorkor or marasmus. The evidence from India (Gopalan 1968) suggests that individual variability must be important, but quantitative data on energy and protein intakes in groups of children developing either kwashiorkor or marasmus within the same community are not available.

Importance of Energy Intakes in Adaptation

In their prospective study of Ugandan children, Rutishauser & Whitehead (1972) found that the children's energy intakes were sometimes surprisingly low. Despite low intakes the children adapted by remaining very inactive and often managed to grow. However, sustained growth on these diets was often accompanied by a slow fall in the concentration of serum albumin; as the albumin levels fell the children became increasingly susceptible to kwashiorkor. This observation led Whitehead (1971) to re-emphasize the importance of measuring serum albumin as an index of nutritional state and to suggest that the dietary amino acids were being preferentially channelled to the periphery by the action of insulin. High insulin levels were therefore effectively depriving the liver of the input of amino acids needed for the synthesis of export proteins. A further restriction on energy intake would lead to a fall in plasma insulin levels and allow a more sustained supply of amino acids to reach the liver. Thus Whitehead viewed the distinction between Kwashiorkor and marasmus as one relating to energy intakes and to the insulin responses on a diet which might be qualitatively similar in both groups of children.

Recent Developments

Essential fatty acid deficiency: Dietary protein and/or energy deficiency alone may not account for all the manifestations of kwashiorkor. Naismith (1973), working in Nigeria, showed that essential fatty acid (EFA) deficiency seemed to be a factor in his cases of kwashiorkor, despite the presence of linoleic acid in the staple diet of maize used in this community as an infant food. He concluded that in the preparation of the food there had been a marked loss of linoleic acid so that intakes were inadequate for a growing child. Plasma concentrations of linoleic acid were low and there was a rise in the unusual metabolite of oleic acid, eicosatrienoic

Table 1

Albumin metabolism in marasmic and recovered children fed high and low protein isoenergetic diets.
(Recalculated from James & Hay 1968)

Protein intake (g/kg/d)	Albumin synthesis (% per day)	Albumin leaving intravascular pool (% per day)	
		Net loss to tissues	Catabolism
Malnourished:			
High (3.3–5.0)	14.5	+3.2	10.1
Low (0.7–1.2)	5.7	−5.7	9.4
Recovered:			
High (3.3–5.0)	13.9	+0.6	13.5
Low (0.7–1.2)	9.4	−3.1	10.8

acid, which is characteristically found in animals and humans consuming a diet low in essential fatty acids. Although Naismith did not seem to consider EFA deficiency to be of great importance, further documentation of this nutritional component of the disease is needed, since the syndrome of kwashiorkor has many of the features found in animal studies on EFA deficiency. These include skin rashes, dyspigmented skin, thin hair, fatty liver with decreased protein synthesis, gut lesions, increased capillary permeability and an enhanced susceptibility to infections (Holman 1971).

Since there seems to be a very marked fall in linoleic acid levels during stress (Troll & Rittmeyer 1974), linoleic acid may need to be provided in increased amounts for a child living in a tropical environment where infections are so frequent.

Infections and EFA deficiency may both accentuate hypoalbuminæmia. Serum albumin levels depend not only on the balance between the rates of albumin synthesis and catabolism, but also on the distribution of albumin between the intravascular and extravascular compartments (James & Hay 1968). Malnourished children adapt by reducing their catabolic rates and by limiting the extravascular distribution of albumin. EFA deficiency, by affecting capillary permeability, could not only increase the transcapillary escape of albumin, but thereby increase albumin catabolism if the transcapillary escape rate of albumin is related to albumin catabolism (Rossing *et al.* 1976). Albumin loss into the gut increases if there is intestinal damage and this loss is accentuated by infections, particularly measles. Infections also depress albumin synthesis by inducing anorexia and reducing the intake of protein and energy.
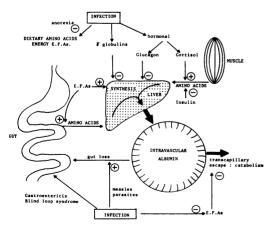
Changing hormone levels in response to infection, e.g. a rise in plasma glucagon, will further depress albumin synthesis and the rise in γ-globulins may exert a depressing effect as the plasma oncotic pressure rises (Coward 1975). All these events involve complex interactions on albumin metabolism which are summarized in Fig 1.

If EFA deficiency proves to be an important component of the syndrome of kwashiorkor, then this deficiency is readily preventable. The application of EFAs to the skin will overcome both the skin rashes and the systemic manifestations of EFA deficiency (Press *et al.* 1974), and even the treatment of an EFA-deficient child with gastroenteritis will be possible. It may be relevant to note that oiling the skin of children and adults is part of the cultural tradition in many tropical countries where fat intakes are low. Many studies of the dietary management of children with kwashiorkor have failed to take account of the concomitant oiling of the skin, which is considered a routine part of the nursing care of an ill child with a dry scaling skin.

Gut in malnutrition: In 1966 Brunser and his colleagues (Brunser *et al.* 1966) showed that children with kwashiorkor in Chile had a very abnormal gut mucosa with atrophy and cellular infiltration of the jejunal villi; in contrast, children with marked nutritional dwarfing, i.e. marasmus, had an almost normal mucosa. Studies in Jamaica also showed that there were differences in the disaccharidases activities of children with and without œdema (James 1971). Dammin (1965) had found in post-mortem studies on malnourished Mexican children that they had a marked proliferation of organisms in the small intestine. *In vivo* studies were therefore begun in Jamaica to confirm these findings (James *et al.* 1972). Detailed studies with cultural techniques appropriate for both aerobic and anaerobic organisms failed to show very high numbers of organisms in marasmic children with or without acute gastroenteritis. No specific enterotoxin-producing *E. coli* or bacteroides capable of deconjugating bile salts were isolated. Measurements of the bile salts' concentrations before and after meals also showed that these children had perfectly normal levels, well above the critical micellar concentration and there was no evidence of deconjugation of the bile acids (Table 2).

In marked contrast to these findings were the observations on children with kwashiorkor in Guatemala (Schneider *et al.* 1974). Large numbers of anaerobic bacteroides were isolated from jejunal aspirates and high concentrations of free bile acids were also observed. The findings were therefore very similar to those seen in the blind-loop syndrome. Fat malabsorption is known to occur in

Fig 1 *Interactions of nutrients and infection and their effects on albumin metabolism. Effect of a hormone or nutrient on flow of amino acids and protein is designated as either* $\ominus$ *i.e. increasing flow, or* $\oplus$ *when transport is limited*

Table 2

Mean duodenal bile acid levels in kwashiorkor and marasmus

Country	Nutritional state	Bile acids ($\mu mol/g$ fluid)	
		Conjugated	Free
Guatemala●	Kwashiorkor	2.9	0.8
	Recovered	8.3	1.4
Jamaica■	Marasmus	7.9	Not detected
	Recovered	5.9	Not detected

● Schneider & Viteri (1974)
■ James & Wiggins (unpublished)

malnutrition and could limit the absorption of EFAs. In addition, the availability of linoleic acid may be reduced by its metabolism by jejunal bacteria. Thus, a blind-loop syndrome may be a critical feature of some children with kwashiorkor and affect not only fat absorption but also the digestion and absorption of amino acids from dietary protein. Studies performed more recently in Asia (Gracey *et al.* 1973) and in the Gambia (Heyworth & Brown 1975) have not distinguished between cases of kwashiorkor and marasmus (Table 3), but additional information is emerging to suggest that gut contamination by bile-splitting organisms and other anaerobes may be an important complication which limits the absorption of nutrients in these ill and malnourished children who are already existing on marginal intakes of food.

Immune function in malnutrition: For many years it has been recognized that the malnourished child has an increased susceptibility to infection (Scrimshaw *et al.* 1968) and over the last five years there have been a number of detailed studies showing that malnourished children have an impaired immunological system. This impairment includes abnormalities of phagocytic function, an inability to produce circulating immunoglobulins to specific antigenic stimuli, a failure to produce specific secretory IgA in response to immunization (Chandra 1975), a failure of cell-mediated immunity with a reduction in the lymphocyte population (particularly those derived from the thymus),

and a poor response to both lymphocyte stimulation and skin testing for hypersensitivity (Smythe *et al.* 1971, Edelman *et al.* 1973). In addition, abnormalities have been found in complement function and in opsonin and transferrin metabolism. Thus almost every system involved in the response to infection seems to be affected. Indian studies have suggested that many of these immunological deficiencies only become functionally important in children with severe growth retardation (Reddy *et al.* 1976). If these studies are confirmed then immunological testing may become an important part of the assessment of nutritional state, since the results will determine the level of growth retardation at which nutritional support is required. It must, however, be recognized that the finding of impaired immunological responses in children with malnutrition does not necessarily mean that the deficient protein or energy content of the diet is primarily responsible for these changes. Animals fed a low protein diet often fail to show immunological deficiencies (Cooper *et al.* 1974) and it has recently been found that a range of immunological abnormalities can occur in both iron and folic acid deficiency (Chandra & Saraya 1975, Coovadia *et al.* 1974 Gross *et al.* 1975). It is often not realized that many children with protein-energy malnutrition have concomitant iron and folate deficiency. Folate deficiency, in particular, has not been investigated systematically as a complication of malnutrition, and if iron and folic acid deficiency prove to be of importance in determining the host response to infections, then clearly greater emphasis will need to be given to increasing these nutrients in the diet and providing them in a form available for absorption.

Conclusion

For the last thirty years there has been controversy surrounding the classification and causes of malnutrition in children. The relative importance of protein and energy supply and the interactions between protein and energy metabolism are still being worked out. Laboratory studies often fail to include the additional effects of infections to which children are frequently exposed in a tropical en-

Table 3

Duodenal and jejunal microflora in malnutrition

Country	Reference	Bacterial counts●		% children with:	
		Aerobic	Anaerobic	E. coli	Bacteroides
Jamaica	James *et al.* (1972)	1.6 ± 1.7	2.0 ± 2.0	100	0
Guatemala	Mata *et al.* (1972)	6.5 ± 1.7	6.1 ± 1.7	50	30
Indonesia	Gracey *et al.* (1973)	5.5 ± 0.5	2.0 ± 0.5	35	30
Gambia	Heyworth & Brown (1975)	6.3 ± 1.1	—	—	—
Argentina	Fagundes Neto *et al.* (1976)	6.3 ± 1.1	—	—	—

● Mean ± SEM $\log_{10}$ bacteria/ml fluid

vironment. As clinical investigations continue it is becoming apparent that the problems of malnutrition are even more diverse than was at first thought and that other nutritional deficiency states must now be considered as important associated features of protein-energy malnutrition. The availability of essential fatty acids, iron and folic acid may all be limited and deficiencies of these nutrients deserve greater consideration. Attempts on a national or an international level to increase the protein and/or energy supply to the diet have had little success in reducing the prevalence of malnutrition and it would seem, therefore, that continued study of the condition is warranted. Public health measures depend upon an accurate understanding of the nutritional as well as social and economic factors involved in the development of protein-energy malnutrition. The role of intestinal infections and jejunal bacterial overgrowth may prove a key to further developments in understanding the prevalence of malnutrition.

REFERENCES
Ashworth A, Bell R, James W P T & Waterlow J C
(1968) *Lancet* ii, 600
Autret M & Béhar M
(1954) Food and Agriculture Organization
Nutritional Studies No. 13
Brock J F, Hansen J D L, Howe E E *et al.*
(1955) *Lancet* ii, 355
Brunser O, Reid A, Mönckeberg F *et al.*
(1966) *Pediatrics* 38, 605
Chandra R K
(1975) *British Medical Journal* ii, 583
Chandra R K & Saraya A K
(1975) *Journal of Pediatrics* 86, 899
Cooper W C, Good R A & Mariani T
(1974) *American Journal of Clinical Nutrition* 27, 647
Coovadia H M, Parent M A, Loening W E K *et al.*
(1974) *American Journal of Clinical Nutrition* 27, 665
Coward W A
(1975) *British Journal of Nutrition* 34, 459
Dammin G J
(1965) *Federation Proceedings* 24, 35
Edelman R, Suskind R, Sirisinha S & Olson R
(1973) *Lancet* ii, 506
Fagundes Neto U, Toccalino H & Dujovney F
(1967) *Acta Pædiatrica Scandinavica* 65, 609
Gopalan C
(1968) In: Calorie Deficiencies and Protein
Deficiencies. Ed. R A McCance & E M Widdowson.
Churchill, London; p 49
Gracey M, Suharjono, Sunoto & Stone D F
(1973) *American Journal of Clinical Nutrition* 26, 1170
Gross R L, Reid J V O, Newberne P M *et al.*
(1975) *American Journal of Clinical Nutrition* 28, 225
Heyworth B & Brown J
(1975) *Archives of Disease in Childhood* 50, 27
Holman R T
(1971) In: Progress in the Chemistry of Fats and other Lipids,
vol 9. Ed. R T Holman. Pergamon, Oxford; p 275
James W P T
(1971) *Archives of Disease in Childhood* 46, 218
James W P T, Drasar B S & Miller C
(1972) *American Journal of Clinical Nutrition* 25, 564
James W P T & Hay A M
(1968) *Journal of Clinical Investigation* 47, 1958
Jelliffe D B
(1959) *Journal of Pædiatrics* 54, 227
Mata L J, Jiménex F, Cordón M *et al.*
(1972) *American Journal of Clinical Nutrition* 25, 1118
McCance R A
(1968) In: Calorie Deficiencies and Protein Deficiencies.
Ed. R A McCance & E M Widdowson. Churchill, London; p 1
Naismith D
(1973) *British Journal of Nutrition* 30, 567
Press M, Hartop P J & Prottey C
(1974) *Lancet* ii, 597
Reddy V, Jagadeesen V, Ragharamulu N *et al.*
(1976) *American Journal of Clinical Nutrition* 29, 3
Rossing N, Parving H-H & Lassen N A
(1976) In: Plasma Protein Turnover. Ed. R Bianchi, G Mariani
& A S McFarlane. Macmillan, London; p 357
Rutishauser I H E & Whitehead R G
(1972) *British Journal of Nutrition* 28, 145
Schneider R E & Viteri F E
(1974) *American Journal of Clinical Nutrition* 27, 788
Scrimshaw N S, Taylor C E & Gordon J E
(1968) WHO Monograph Series No. 57.
World Health Organization, Geneva
Smythe P, Schonland M, Brereton-Stiles G G *et al.*
(1971) *Lancet* ii, 939
Troll V & Rittmeyer P
(1974) *Infusionstherapie* 3, 230
Waterlow J C
(1968) *Lancet* ii, 1091
Waterlow J C, Cravioto J & Stephen J M L
(1960) *Advances in Protein Chemistry* 15, 131
Whitehead R G
(1971) In: Proceedings of the XIII International Congress of
Pediatrics, Vienna, vol. 2 part 1. Wiener Medizinischen
Akademie, Vienna; p 231
Williams C D
(1933) *Archives of Disease in Childhood* 8, 423

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Malnutrition in the Elderly

The individual dietary patterns in the majority of old people remain similar to those which have been acquired by habits established at a younger age. Nevertheless, there are many factors which begin to operate more frequently with advancing age and these may lead to nutritional deficiencies. Some of these factors are related to decline in bodily health with difficulty in obtaining and preparing food; to changed economic circumstances resulting from retirement; to depression and organic mental deterioration; to social isolation and loneliness, especially following bereavement; and to ignorance of what constitutes a balanced diet, particularly in the widower who must often cater for himself for the first time. The primary and secondary causes of malnutrition in old age are summarized in Table 1.

In any one individual malnutrition is often multifactorial in origin, especially in the housebound old person who, in addition to physical ill-health, may suffer from social isolation, straitened financial circumstances and impaired appetite due